Actions to Advance the Development and Adoption of Abuse-Deterrent Opioids

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On behalf of the Branded Industry Working Group

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Introduction

- The rising prevalence of chronic pain and the increasing use and abuse of opioid analgesics have created an epidemic of distress, disability and danger to a large percentage of Americans[1,2,3]
- Numerous sponsors are working to develop new, powerful but safe, non-opioid alternatives to treat pain, however, until these new treatments become available, opioid analgesics will remain an indispensable component of pain therapy
- The working group shares the FDA's vision of the future in which most or all opioid analgesics are available to pain patients who need them in formulations that are less susceptible to abuse
  - The time to act on the crisis of opioid abuse, misuse, diversion, overdose and death is now
- The FDA has spearheaded the effort to foster the development and use of abuse-deterrent opioids, but more can and should be done
- Concerted action by numerous stakeholders in addition to the FDA is required to achieve broad adoption of opioids with meaningful abuse-deterrent properties

1. IOM. *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington, DC: The National Academies Press; 2011.
2. CDC. *Primary Care and Public Health Initiative. Prescription Drug Abuse and Overdose: Public Health Perspective*. October 24, 2012. Data from Source™ Prescription Audit (SPA) & IMS Health Vector One®: National (VONA).
3. CDC. *MMWR Morb Mortal Wkly Rep*. 2013;62(12):234.

The Branded Industry Working Group Recommendations

1. The FDA should implement prominent labeling to distinguish between abuse-deterrent and non-deterrent products, in order to inform and motivate preferential use of the former, and to encourage innovation
2. Meaningful abuse-deterrent properties should be defined as those supporting a claim that ‘a product is expected to result in a meaningful reduction in abuse’ for a given route of abuse (Tier 3 labeling)
3. The FDA should not approve new opioids or opioid formulations that lack meaningful abuse-deterrent properties, unless the new entrant fulfills an unmet clinical need or provides a unique therapeutic benefit
4. Upon approval of new products with meaningful abuse-deterrent properties, the FDA should re-assess the risk-benefit of previously marketed non-abuse-deterrent versions; if the benefits of non-abuse-deterrent products no longer outweigh their risks, the FDA should require their sponsors to withdraw, for safety reasons, both branded and generic versions within 2-3 years
   - The sponsors of such products can submit new data to support abuse-deterrent labeling
5. Tier 3 abuse-deterrent labeling as a minimum should be sufficient to action withdrawal of the non-abuse-deterrent versions
6. The FDA should clarify the development path(s) through guidances and work with Congress to address the limited and uncertain intellectual property protection for abuse-deterrent opioids
7. HHS, including FDA and CMS, should create stronger mandates and policies to support patient access to opioid analgesics with meaningful abuse-deterrent properties and to other pain therapies

Chronic Pain and Opioid Abuse Demand Action

- The high prevalence and complexity of chronic pain, combined with the need to provide care for patients with pain, have contributed to the increased use and availability of opioid analgesics, and the associated rise in prescription opioid abuse, overdose and deaths[1,2]
- Health care professionals do not receive sufficient training in clinical management of chronic pain patients and appropriate opioid prescribing[3]
- Identifying and predicting the misuse and abuse of opioid analgesics is challenging[4,5]
- Abuse-deterrent opioid analgesics are designed to provide patients the same pain relief as opioids without such properties, while helping to reduce abuse via tampering, the most deadly form of abuse[6]
- It is imperative that universal adoption of abuse-deterrent opioids be considered an integral part of a comprehensive approach to responsible opioid prescribing which also includes
  - Mandatory use of PDMPs, careful monitoring of treatment effectiveness and patient behavior, medical provider education, etc.

1. IOM. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press; 2011.
2. CDC. Primary Care and Public Health Initiative. Prescription Drug Abuse and Overdose: Public Health Perspective. October 24, 2012. Data from Source™ Prescription Audit (SPA) & IMS Health Vector One®: National (VONA).
3. Poon SJ et al. *Ann Emerg Med*. 2014;64:490-495.
4. Brown J et al. *J Opioid Manag*. 2011;7(6):467-483.
5. Turk DC et al. *Clin J Pain*. 2008;24(6):497-508.
6. Katz N et al. *Am J Drug Alcohol Abuse.* 2011;37(4):205-217.

Labeling is Essential to Fostering Development and Use of Abuse-Deterrent Opioids

- We recommend that the FDA implement prominent labeling to distinguish between abuse-deterrent and non-abuse-deterrent products, in order to
  - Address the low awareness of the availability of abuse-deterrent opioid analgesics on the part of clinicians, payers, and patients[1]
  - Motivate preferential use of abuse-deterrent analgesics where appropriate
- Labeling can also help encourage the use of abuse-deterrent opioid analgesics by discouraging the use of non-abuse-deterrent products, provided that patient needs are met
- Additional labeling amendments may be required to direct clinicians to use abuse-deterrent products preferentially, and to address the following barriers
  - Many clinicians underestimate the risks of abuse and diversion[2,3], and may be reluctant to switch a patient to a new technology which offers no efficacy advantage
  - Existing payment structures and incentives favor the currently available largely generic and non-abuse-deterrent opioid analgesics[4,5]

1. Pfizer Data on File. ATU Study, July 2013.
2. Brown J et al. *J Opioid Manag*. 2011;7(6):467-483.
3. McDonald DC et al. *PLOS One*. 2013;8(7): e69241.
4. NIH Pathways to Prevention Workshop: The Role of Opioids in the treatment of Chronic Pain, Sept 29-30, 2014, Draft Statement.
5. http://www.fingertipformulary.com/Home/ accessed October 2014.

What Are Meaningful Abuse-Deterrent Properties?

- Meaningful abuse-deterrent properties should be defined as those supporting a claim that 'a product is expected to result in a meaningful reduction in abuse' (Tier 3 labeling)[1] for a given route of abuse
  - Based on the reduction in abuse potential in human abuse liability (Category 3) studies, and supported by in vitro and pharmacokinetic data (Category 1 and 2)
- While highly desirable, the goal of acquiring post-marketing (Category 4) data is inaccessible for newly approved opioid analgesics with meaningful abuse-deterrent properties
  - The time needed to obtain such data is uncertain in view of the current barriers to sufficient new drug utilization
  - The sources of post-marketing data have critical limitations (inability to identify individual products/routes of abuse/methods of tampering, under-reporting, inadequate coding and data capture, etc.)[2]

1. FDA's draft guidance, Abuse-Deterrent Opioids – Evaluation and Labeling, 2013, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf
2. Secora AM et al. *Pharmacoepidemiology and Drug Safety* 2014; Sep 25.

Refusal to Approve a New Opioid Lacking Meaningful Abuse-Deterrent Properties

- The FDA should not approve new opioids or opioid formulations that lack meaningful abuse-deterrent properties unless they fulfill an unmet need or provide a unique therapeutic benefit

- FDA should encourage and support, through the development of guidance documents, a transition of all opioid products, both immediate and extended release, towards abuse-deterrent forms

- Development of novel opioid analgesics or formulations that deter abuse via oral overconsumption is the focus of multiple ongoing efforts, however this goal has so far remained elusive

Withdrawal of Currently Marketed Opioids Lacking Meaningful Abuse-Deterrent Properties

- Upon approval of new opioid analgesics with meaningful abuse-deterrent properties, the FDA should re-assess the risk-benefit of previously marketed non-abuse-deterrent versions*
- If the benefits of the non-abuse-deterrent opioid(s) no longer outweigh their risks, the FDA should require the sponsors, within 2-3 years, to withdraw for safety reasons both branded and generic versions of such products
  - The sponsors of such products can submit new data to support abuse-deterrent labeling
- The withdrawal should be contingent on
  - The new product with meaningful abuse-deterrent properties meeting the efficacy and safety needs of the pain patient, and maintaining its overall risk-benefit profile
  - The sponsor of the new product with meaningful abuse-deterrent properties working with the FDA and DEA to provide mitigation supply agreements against drug shortages
- Where the FDA has the authority to act they should take action; where they do not, the FDA should work with stakeholders to obtain the requisite authority

*Containing a particular opioid molecule with the same time release profile and duration (IR, ER 12hrs, ER 24hrs, etc.), route of administration (patch, oral), and indication (acute or chronic pain) as the previously marketed version

Other Proposed FDA Actions to Encourage Investment in the Development of New and Better Opioids with Meaningful Abuse-Deterrent Properties

- Provide clear guidance requiring the preservation of abuse-deterrent characteristics by generic manufacturers
- Provide guidance on demonstrating superiority/non-inferiority in head-to-head human abuse liability studies and on how to communicate the data in the label
- The FDA should work with Congress to provide extended data exclusivity for products with meaningful abuse-deterrent properties
- The FDA has used exclusivity and vouchers to foster development in other medication categories, for example
  - 6-months pediatric exclusivity add-on[1]
  - 5-year regulatory exclusivity add-on pursuant to Generating Antibiotic Incentives Now Act ("GAIN Act")[2]
  - Tradable priority review vouchers under the Rare Pediatric Disease[3] and Tropical Disease[4] acts

1. FD&C Act Sec. 505A.
2. FD&C Act Sec. 505E.
3. FD&C Act Sec. 529.
4. FD&C Act Sec. 524.

Current Reimbursement Environment Impedes the Transition to Abuse-Deterrent Opioids

- We request that HHS, including FDA and CMS, create stronger mandates and policies to support patient access to opioid analgesics with meaningful abuse-deterrent properties and to other pain therapies
- Existing payment structures help illustrate system-wide barriers to the adoption of new pain therapies and treatment modalities and to the appropriate management of patients with pain, for example[1,2]
  - Non-opioid analgesics are uniformly recommended as first-line treatments, however patient access to the branded non-opioid analgesics is often restricted with prior authorizations / step-edits and higher patient co-pays and co-insurance[1,2]
  - In contrast, patient access to currently available largely generic opioid analgesics is unrestricted[1,2]
  - Furthermore, patient access to chronic care pain management team is rarely reimbursed[1]
- These policies, which disadvantage appropriate first-line therapies and provide preferential patient access to the currently available, largely generic and non-abuse-deterrent opioids, contribute to opioid overprescribing and are likely to delay, if not prevent, the adoption of abuse-deterrent opioids

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Concluding Remarks

- Developing opioid analgesics with meaningful abuse-deterrent properties is an enormous challenge from a pharmaceutical perspective, to deliver on two opposing goals
  - Achieve the same release profile as the reference product without abuse-deterrent properties to ensure comparable analgesia *when taken as directed*
  - Prevent the release or counteract the effect of the opioid agent (i.e., display abuse-deterrent properties) *only when the product is manipulated for abuse*

- Individual companies would welcome an opportunity to participate in additional discussions regarding the complex scientific, regulatory, medical, and policy issues associated with abuse-deterrent opioids

- Given the crisis of opioid abuse, the time is now to advance the shared vision of a future in which most or all opioid analgesics are available to pain patients who need them in formulations that are less susceptible to abuse